PATENT
Docket No. SALK1650-2
(088802-2753)

REMARKS

The presently claimed invention offers novel and nonobvious methods for treating individuals with diabetes mellitus or for modulating expression of genes encoding liver proteins that play a role in this disease. Common to all methods is the administration of an inhibitor of the interaction between the cAMP responsive transcriptional activator CREB and CBP, a protein that binds to the phosphorylated (i.e., activated) form of CREB and mediates cAMP responsive transcription.

Claims 1, 7, 12 and 17-33 are presently presented.

Rejection under 35 U.S.C. § 112, first paragraph

A. Written Description

The rejection of claims 1, 7, 12 and 17-34 under 35 U.S.C. § 112, first paragraph for allegedly lacking written description is respectfully traversed.

The proper standard for determining compliance with the written description requirement of 35 U.S.C. § 112, first paragraph, is whether the specification reasonably conveys to the skilled artisan that the inventor was in possession of the claimed invention as of the filing date. *See* MPEP § 2163.02 (citing *Ralston Purina Co. v. Far-Mar-Co., Inc.*, 227 USPQ 177, 179 (Fed. Cir. 1985)). The subject matter of the claimed invention need not be described literally in the specification in order to satisfy the requirements of 35 U.S.C. § 112, first paragraph. *Id.* In a careful analysis of the written description requirement provided by the Patent and Trademark Office in its *Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112 ¶1. "Written Description" Requirement*, it is stated that an adequate written description "may be shown by any description of sufficient, relevant, identifying characteristics so long as a person skilled in the art would recognize that the inventor had possession of the claimed invention." 66 Fed. Reg. 1099, 1105 (2001) (emphasis added).

As a threshold matter, it is noted that the claims are directed to three different aspects of the invention, i.e., claims 1-7, 12 and 17 are directed to methods of diabetes treatment; claims 18-24 and 33 are directed to methods for modulating glucose metabolism in an individual; and claims 25-32 are directed to methods of inhibiting the expression of carboxykinase (PEPCK) enzyme in an individual. Even though all of the Examiner's attempts to suggest this rejection are directed specifically to methods to treat diabetes, Applicant assumes that the written description rejection as applied to claims 1-7, 12 and 17 was also intended to apply to claims 18-33. Clarification of the record is respectively requested if the assumption is incorrect.

The crux of the rejection, in the Examiner's words, appears to be that the "specification does not describe or disclose the structure of even one compound that has been identified by Applicant's method and treats diabetes. Paper No. 25, page 5. The Examiner alleges that only functional characteristics are given, that being "to disrupt or inhibit binding of CREB to CBP." Paper No. 25, page 5.

First, the Examiner has cited to no law for the extreme proposition that written description requires a chemical structure in the case of a method that uses a compound where the identity of the compound can be identified by methods extensively described and admitted by the Examiner to be enabling. Second, the Examiner is incorrect that the specification does not "disclose the structure of even one compound." In this regard, the specification discloses the structure of many inhibitory compounds in the paragraph bridging pages 15 and 16.

> Compounds which are capable of inhibiting activation of cAMP and mitogen responsive genes, and hence can be identified by the invention assay method, include antibodies raised against the binding domain of the protein set forth in SEQ ID NO:2, antibodies raised against the binding domain of CBP-like compounds, and the like. Presently preferred antibodies are those raised against a polypeptide fragment comprising amino acid residues from about 461 up to 661 of the protein set forth in SEQ ID NO:2; with antibodies raised against a polypeptide fragment comprising amino acid residues from about 634 up to 648 of the protein set forth in SEQ ID NO:2 (this subfragment is also set forth specifically as SEQ ID NO:3), being especially preferred. Alternatively, antibodies which are raised against the amino acid

> residues surrounding residue 600 of CBP (see SEQ ID NO:2) or antibodies which inhibit the phosphorylation of residue 133 of CREB are also desired (see, for example, Parker et al., Mol Cell Biol (1996) 16(2):694-703).

The above passage describes antibody compounds that disrupt CREB:CBP interaction and, hence, inhibit activation of cAMP and mitogen responsive genes. The structure of an antibody is well known and is described in reference to what it binds. Furthermore, page 17, first full paragraph of the application, discloses the structure of additional inhibitory compounds.

> Alternative compounds which are capable of inhibiting activation of cAMP and mitogen responsive genes include polypeptide fragments comprising amino acid residues from about 461 up to 661 of the protein set forth in SEQ ID NO:2. Polypeptide fragments comprising amino acid residues set forth specifically as SEQ ID NO:3 or KIX polypeptide fragments having a mutation at residue 600 (Arg-600), set forth in SEQ ID NO:2, are preferred, while KIX polypeptide fragments substituting Gln for Arg-600 are presently most preferred. Other polypeptide fragments contemplated for use in the practice of the present invention include those comprising the KID domain, preferably those comprising residue 133 of CREB. In the most preferred CREB polypeptide fragment, serine residue 133 is mutated to an amino acid residue which can not be phosphorylated. Other compounds which inhibit CREB activity (i.e., phosphorylated-Ser133) by binding to CBP include adenovirus E1A oncoprotein (Nakajima et al. Genes Dev (1997) 11(6):738-747), and the like. Those of skill in the art will readily recognize other polypeptide fragments which will readily inhibit the formation of CREB:CBP complex employing such assays as those disclosed herein.

This passage describes peptide fragment inhibitory compounds including the KIX and KID domains and mutated forms of the peptides. Precise structures of the compounds are provided by reference to specific sequences (see citations to SEQ ID NOS.). The adenovirus E1A oncoprotein is also mentioned as a CREB:CPB interaction inhibitor.

Thus, the application fully describes a method of diabetes treatment and modulating glucose metabolism or inhibiting PEPCK through the administration of compounds that disrupt interaction of CREB with CBP. The application also describes numerous exemplary compounds. It is respectfully submitted that one skilled in the art would agree that the inventor was "in possession of the claimed invention." Because the written description requirement of 35 U.S.C. § 112, first paragraph, has been met, Applicants respectfully request that the rejection be reconsidered and withdrawn.

B. Enablement Rejection

The rejection of claims 1, 7, 12 and 17-34 under 35 U.S.C. § 112, first paragraph, for allegedly lacking enablement is respectfully traversed.

The standard for determining enablement is whether the specification as filed provides sufficient information to permit one skilled in the art to make and use the claimed invention. *United States v. Telectronics, Inc.*, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988). The test of enablement is not whether experimentation is necessary, but rather whether any experimentation that is necessary is undue. *Id.* A considerable amount of experimentation is permitted, provided that it is merely routine, or provided that the specification provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

Furthermore, under Patent Office practice, a patent specification is considered to be in compliance with the enabling requirement of § 112, first paragraph, unless there is reason to doubt the objective truth of the statements contained therein. Thus, the Examiner carries the initial burden to substantiate a rejection for lack of enablement. In *re Marzocchi*, 439 F.2d 220, 223-24 (CCPA 1971). In accordance with the burden, the Patent Office must explain why the truth or accuracy of any statement in the specification is doubted and "back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement."

Id.; see also, *In re Richard Sichert*, 566 F2.d 1154, 1161 (CCPA 1977)) ("The PTO has cited to no evidence or reference that contradicts or is inconsistent with any supporting statement of the disclosure.").

Claims 1-7, 12, and 17 are adequately supported by an enabling disclosure

It is respectfully submitted that the Examiner has failed to state a prima facie rejection for enablement. The rejection is deficient in failing to address most of the Wands factors. Furthermore, the Examiner imposes an improper standard of enablement that does not comport with settled law when concluding that Applicant's submission of proof of enablement in the form of the Mayr et al. reference is insufficient because it "does not teach that a compound identified by Applicant's method has a beneficial effect when used to treat diabetes." Paper No. 23, page 10 (see also similar statement bridging pages 10 and 11 re the Herzig et al. reference). It is respectfully submitted that a proper review of the Wands factors and application of an appropriate standard demonstrates enablement of the claims 1-7, 12 and 17.

Nature of the Invention

The claims at issue are directed to a method for treating an individual suffering from diabetes mellitus by administering a compound that disrupts the interaction between CREB and CBP. The compounds are identified by functional language or by an assay which describes how to identify useful compounds. As already discussed above, the specification describes numerous exemplary compounds including antibodies and peptides that will bind either to CREB or to CBP and will disrupt the interaction which is critical to activation of cAMP and mitogen responsive genes involved in diabetes.

State of the Prior Art

The prior art is replete with examples where drugs that affect intracellular events have a beneficial impact in disease treatment. Nearly the entire pharmaceutical industry is based on this principle. Particularly relevant to the instant case is the well established understanding in the prior art of the toxic role played by elevated glucose levels in diabetic individuals. See e.g., Rossetti "Glucose Toxicity: the implications of hyperglycemia in the pathophysiology of diabetes mellitus" *Clin Invest Med* 18(4): 225-260 1995 (citing on page 225 to references 1-7 for the proposition that "substantial evidence linking hyperglycemia to the development and progression of complications associated with diabetes [1-7]") (attached as Exhibit A); *see also* Flatt et al. *Biochemical Society Transactions* 22: 18-23 (1994) (discussing glucose toxicity and role of glycation therein; p.24) (attached as Exhibit B). Thus, Applicant's method of treating diabetes directed to reducing hyperglycemia by modulating aspects of glucose metabolism through disruption of the fundamental CREB:CBP interaction addresses what one skilled in the art would consider to be a predictable route to treating diabetes.

In contrast, the Examiner's sole effort at establishing the state of the prior art is to cite to the Merck Manual, 17th edition, pages 174-176 that discuss treatment of diabetes. It is respectfully submitted that the Merck Manual has little to do with understanding the state of the prior art with respect to enablement of a new diabetes treatment. As previously demonstrated by Applicant, the Merck Manual is not close to being a reliable source for the latest in diabetes treatment methods. The Merck Manual only discusses long established methods of diabetes treatment, mainly treatment using insulin, sulfonylureas, and certain anti-hyperglycemic drugs. Applicant has further supported this view by establishing the fact that the Merck Manual fails to mention any of a larger number of recently patented diabetes treatment methods (a search for "diabetes," "treat" and "method" as claim terms identified 89 issued U.S. patents; a random sampling of these showed that many are directed to new methods of diabetes treatment that are not mentioned in the Merck Manual). For example, U.S. Patent No. 5,561,110 to Michaelis et al. describes and claims carnosine and peptide analogues of carnosine which are useful for treating diabetes mellitus. According to the Michaelis et al. carnosine scavenges reducing sugars in

blood, reducing the level of protein and lipid glycation and toxic effects caused thereby. See Cols. 2 and 3. The Merck Manual cited by the Examiner does not mention treatment with carnosine. In addition, U.S. Patent No. 5,674,900 to Ubillas et al. describes and claims a novel terpenoid-type quinone which are useful for treating diabetes mellitus. According to Ubillas et al. "[n]o compound resembling the structure of the claimed compounds has in any way been associated with the usefulness in the treatment of diabetes mellitus or its sequelae." Col. 3, lines 22-25. The Merck Manual cited by the Examiner also does not mention treatment with terpenoid-type quinones. It is respectfully submitted that the same can be said for the new methods of diabetes mellitus described in U.S. Patent Nos. 5,691,386; 5,700,795; 5,384,032; 5,888,507; 6,146,653; 6,300,349; 6,323,314, all of record in the case.

Accordingly, as shown by a proper review of the state of the prior art, it can be seen that Applicant's method of treating diabetes mellitus addresses what one skilled in the art would consider to be a predicable route to treating diabetes. In contrast, the Examiner's evaluation of the state of the prior art being limited to citation of the Merck Manual, which discusses only long established methods for treating diabetes mellitius, constitutes a clearly deficient analysis of this Wands factor.

Level of one of Ordinary Skill

Applicant respectfully submits that the level of skill in the art of protein-protein interaction inhibitors and their use in complex diseases such as diabetes is high. The Examiner, in contrast, has offered no evidence on this Wands factor.

Considering the objective evidence of record in its entirety, Applicants respectfully submit that the skilled artisan would acknowledge that the level of skill in the art is high for the treatment of diabetes by administering compounds that affect glucose metabolism.

Predictability in the Art

Applicant respectfully submits that the art in the relevant field is reasonably predictable. As indicated from the analysis of the state of the art, there is a great deal known about the role of glucose in diabetes and about the beneficial affects of lowering circulating glucose levels. Applicant's discovery that the CREB:CBP interaction is central to the regulation of glucose metabolism and that compounds which inhibit this interaction are useful in treating diabetes puts the discovery squarely within an approach known to be predicable. The application also provides exemplary inhibitory compounds and methods to identify others that require only routine experimentation. The Examiner, in contrast, has offered no evidence on this Wands factor.

Considering the objective evidence of record in its entirety, Applicants respectfully submit that the skilled artisan would acknowledge that it would be predictable that administering compounds that disrupt interaction between CREB and CBP would be beneficial to the treatment of diabetes.

The Amount of Direction or Guidance Present

The instant specification provides methods to identify a compound that inhibits the interaction of CREB with CBP. Included is a description of various cell lines to use and expression vectors to express the interacting proteins in the form of a functional bioassay. In

fact, inhibiting compounds are described as already discussed and supported by citation herein above. The working examples of the specification provide further enabling support for compound selection methods. With respect to diabetes treatment, for compounds which meet the inventors' criteria, the specification provides a description of suitable routes of administration, methods of formulation, and dosing, the latter including concentration ranges (page 17-18). The Examiner, in contrast, has offered no evidence on this Wands factor.

Considering the objective evidence of record in its entirety, Applicants respectfully submit that the skilled artisan would acknowledge that the specification provides extensive guidance for making compounds and for using them with a reasonable likelihood of success.

Presence of Working Examples

As already mentioned, the working examples of the specification provide further enabling support for compound selection methods. With respect to diabetes treatment, for compounds which meet the inventors' criteria, the specification provides a description of suitable routes of administration, methods of formulation, and dosing, the latter including concentration ranges (page 17-18).

Furthermore, Applicants have cited to Mayr et al. ("Transcriptional Regulation of the Phorphorylation-Dependent Factor CREB" Molec. Cell Biol., 2:599, 2001) and Herzig et al. ("CREB Regulates Hepatic Gluconeogenesis Through the Coactivator PGC-1" Nature 413:179-183, 2001), both of record in the case, for evidence that the claimed invention is enabled as described.

Mayr et al. (Mayr) is a review article published in the prestigious journal, Nature. Mayr makes clear in the Abstract to the article that CREB is involved in control of glucose levels. Mayr, p. 599 (stating that CREB "functions in glucose homeostasis"). Mayr also describes the mechanism by which CREB controls glucose homeostasis, involving phosphorylation of CREB at Ser133, which promotes complexing with the transcriptional co-activator CBP. Mayr, p599, left column and Figure 1a. These conclusions are consistent with Applicant's disclosure

teaching involvement of CREB-CBP complex in diabetes. Furthermore, Herzig et al. ("Herzig") reports that CREB controls glucose homeostasis through expression of gluconeogenic enzymes via the transactivator, PGC-1. Herzig also used normal and diabetic animals to prove that a reduced CREB activity causes fasting hyperglycemia in vivo, a result that Herzig states "is correlated with Type II diabetes." Herzig, page 179 (Abstract).

Therefore, both the Mayr and Herzig articles serve to prove the truth of statements in Applicant's disclosure (i.e., that disruption of CREB-CBP interaction can be used to treat diabetes), rather than to supplement the disclosure itself. See In re Marzocchi, 439 F.2d at 224, n.4 (indicating that references which are not prior art can be used to rebut a prima facie case for lack of enablement if the "question would be regarding the accuracy of a statement in the specification, not whether that statement had been made before.").

The Examiner however, continues to deny that actual results are required, but in effect is requiring that Applicant demonstrate actual results for treatment of diabetes. It is an improper standard of enablement that does not comport with settled law to require Applicant to prove enablement only in the form of actual data that a compound of the invention has a beneficial effect in the treatment of diabetes. The Examiner clearly takes this position by arguing that even accepting Applicant's view that Mayr et al. and Herzig et al. prove that the CREB:CBP interaction plays a critical role in diabetes, enablement is not shown because the references do "not teach that a compound identified by Applicant's method has a beneficial effect when used to treat diabetes." Paper No. 23, page 10 and top of page 11. The question is not whether beneficial effects have been generated, as the Examiner suggests; rather, the question is whether the specification enables the skilled artisan to obtain such affects without undue experimentation. The Examiner has cited to no scientific reasoning to question that the claimed methods of treating diabetes using an inhibitor of CREB:CBP interaction would not be as successful in the treatment of diabetes mellitus as would the approaches used by Mayr et al. and Herzig et al. As described in Exhibit A, reduction in blood glucose levels is considered by the art to be a treatment of diabetes.

Considering the objective evidence of record in its entirety, the skilled artisan would acknowledge that the working examples of the application support enablement of the claims at issue.

Quantitation of Experimentation Necessary

Applicants respectfully submit that the amount of experimentation necessary is not undue. There is no reason to believe that useful inhibitors of the CREB:CBP interaction will not be useful when such compounds reach the targeted components (CREB or CBP) in cells. Only routine experimentation would be needed to identify compounds that function well in this regard.

The Examiner, in contrast, has offered no evidence on this Wands factor. Considering the objective evidence of record in its entirety, Applicants respectfully submit that the skilled artisan would acknowledge that the quantity of experimentation necessary to practice the claimed methods is not undue.

Claims 1-7, 12 and 17 Meet the Enablement Standard of 35 U.S.C. §112, first paragraph.

In view of the objective evidence of record, and the foregoing analysis of the factors set forth in *In re Wands*, Applicant respectfully submits that claims 1-7, 12 and 17 meet the enablement standard of 35 U.S.C. § 112, first paragraph. The Examiner's opinion to the contrary is not founded on a proper Wands analysis and is defective for applying a standard for determining compliance with the enablement requirement that does not comport with the settled law. Because the enablement requirement of 35 U.S.C. § 112, first paragraph, has been met, Applicant respectfully requests that the rejection be reconsidered and withdrawn with respect to Claims 1-7, 12 and 17.

Claims 18-24 and 33 are adequately supported by an enabling disclosure

Claims 18-24 and 33 are directed to modulating glucose metabolism in an individual. Enabling disclosure support can be found, for example, at page 20, lines 1-11, which refers to modulating gluconeogenesis and/or hyperglucagonemia by "employ[ing] compounds which disrupt the formation of CREB:CBP complexes, thus inhibiting the transcription of PEPCK or glucogon gene."

It is respectfully submitted that that no prima facie rejection for lack of enablement has been stated. The Examiner has chosen to lump claims 18-24 and 33 together with claims 1-7, 12 and 17 for the presumed convenience of applying the same rejection to these separate claim groupings. As applied, the Examiner is rejecting claims 18-24 and 33 on the ground that treatment of diabetes mellitus is not enabled. However, claims 18-24 and 33 make no reference whatsoever to diabetes mellitus.

Thus, the rejection is clearly deficient on its face, over and above the deficiencies already discussed with respect to claims 1-7, 12 and 17. Furthermore, as no analysis of the Wands factors has been made, Applicant has nothing to rebut. Because the Examiner has failed to meet the burden of challenging enablement of claims 18-24 and 33, Applicants respectfully request that the rejection be reconsidered and withdrawn.

Claims 25-32 are adequately supported by an enabling disclosure

Claims 25-32 are directed to a method for inhibiting expression of phosphoenolpyruvate carboxylkinase (PEPCK) enzyme in an individual. Written description support can be found, for example, at page 20, lines 1-11, which refers to modulating gluconeogenesis and/or hyperglucagonemia by "employ[ing] compounds which disrupt the formation of CREB:CBP complexes, thus inhibiting the transcription of PEPCK or glucogon gene."

It is respectfully submitted that that no prima facie rejection for enablement has been stated. The Examiner has chosen to lump claims 25-32 together with claims 1-7, 12 and 17 for the presumed convenience of applying the same rejection to these separate claim groupings. As applied, the Examiner is rejecting claims 25-32 on the ground that treatment of diabetes mellitus is not enabled. However, claims 25-32 make no reference whatsoever to diabetes mellitus.

Thus, the rejection is clearly deficient on its face, over and above the deficiencies already discussed with respect to claims 1-7, 12 and 17. Furthermore, as no analysis of the Wands factors has been made, Applicant has nothing to rebut. Because the Examiner has failed to meet the burden of challenging enablement of claims 25-32, Applicants respectfully request that the rejection be reconsidered and withdrawn.

SUMMARY

It is respectfully submitted that the application is in condition for allowance. Accordingly, reconsideration and favorable action on all the claims is respectfully requested.

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In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, Applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 50-0872**. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Respectfully submitted,

Date September 11, 2003

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